ASBMT Best Abstract Awards for Basic Science

Each year the American Society for Blood and Marrow Transplantation presents Best Abstract Awards to recognize outstanding research in the basic sciences that contribute to the advancement of the field of blood and marrow transplantation. The abstracts receiving the award are those that were scored highest by the Abstract Review Committees. Each award is accompanied by a prize of $1,000. The awards are supported by an unrestricted educational grant from Pfizer Inc.

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GENETIC POLYMORPHISMS IN THE GENES ENCODING HUMAN INTERLEUKIN RECEPTOR 7A (IL-7RA): PROGNOSTIC SIGNIFICANCE IN ALLOGENEIC STEM CELL TRANSPLANTATION (SCT)

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Interleukin-7 (IL-7) belongs to the haematopoietic family of cytokines, being essential for T cell development in the thymus and maintenance of peripheral T cells. IL-7 signals through IL-7R, which consists of a gamma common chain and an alpha-chain. The alpha-chain is also used by the receptor of thymic stromal lymphopoitin (TSLP), a cytokine with complex effects on cytokine profiles including induction of TNF production by dendritic cells. Sequencing of IL-7R-alpha has revealed the existence of 4 single nucleotide polymorphisms (SNPs): (+510C/T, +1237 A/G, 2087T/C and +3110A/G), which all give rise to amino acid substitutions. The aim of the present investigation was to evaluate the significance of IL-7R-alpha SNPs for the outcome and for treatment related complications in allogeneic SCT. **Patients and Methods:** IL-7R-alpha polymorphisms were determined in genomic DNA from 200 recipient and donor pairs from either matched sibling donors or matched unrelated donors (MUD) by an SSP-PCR system. Transplants with mismatch family donors or mismatch unrelated donors were excluded. Genotyping of 173 normal controls was performed in parallel. The indication for SCT included ALL (n = 51), CML (n = 51), AML (n = 51), MDS (n = 12), and various nonmalignant disorders (n=35). **Results:** In MUD transplants, the +1237 genotype of the donor was associated with the survival after SCT, the mortality being highest and intermediate for the GG and AG genotypes, respectively ($P = .043$). This pattern was more pronounced with respect to treatment related mortality ($P = .0042$), while IL-7R-alpha genotypes were unrelated to the risk of relapse of leukaemia. In line with this, the occurrence of GvHD at day +100 was related to the +1237 genotype of the donor (GG [43%], AG [13%], and AA [3%]; $P = .0055$). The IL-7R-alpha +1237 genotypes of the recipient and the genotypes of the other 3 polymorphisms were not significantly associated with the outcome of SCT. **Conclusion:** The presented data suggest that the IL-7 pathway may be of pathogenetic importance for transplant related mortality after SCT. The +1237 polymorphism is located at the extracellular part of IL-7R-alpha, and may influence binding or signalling through IL-7R. Furthermore, this study suggests that selection of donors based on IL-7R-alpha typing, in addition to HLA-typing, may help to reduce treatment related mortality in SCT.

2

MESENCHYMAL STEM CELLS INDUCE DIVISION ARREST ANERGY OF ACTIVATED T CELLS

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It has been demonstrated that bone marrow mesenchymal stem cells (MSC) inhibit T cell responses both to polyclonal stimuli and their cognate antigen. We analyzed the effect of MSC on T cell activation, effector function and proliferation using an in vitro murine model in which T cells were generated against the male HY minor histocompatibility antigen. T cell proliferation and intracellular IFN-γ staining were used to measure T cell responses. In the presence of MSC, early activation markers CD25 and CD69 were found to be up regulated on stimulated T cells, whereas IFN-γ production was inhibited. To determine the effect of MSC on T cell proliferation, CFSE-labeled HY-specific T cells were stimulated with class I-restricted HY peptides. In the presence of MSC the intensity of CFSE-stained T cells remained unchanged demonstrating that T cell proliferation was completely abrogated. Analysis of the cell cycle showed that T cells, stimulated in the presence of MSC, were arrested at the G1 phase. At the molecular level cyclinD2 expression was profoundly inhibited, whereas p27kip1 was upregulated. When MSC were removed from the cultures and restimulated with the cognate peptide, T cells produced IFN-γ but failed to proliferate. The addition of exogenous interleukin-2 did not restore proliferation. MSC did not preferentially target any T cell subset, and the inhibition was also extended to B cells. MSC mediated inhibition induces an unresponsive T cell profile that is fully consistent with that observed in division arrest anergy. Our data have important implications on the clinical use of MSC for tolerance induction.

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IN VIVO FUNCTIONAL IMAGING OF HEMATOPOIETIC STEM CELL ENGRAFTMENT

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Durable hematopoietic stem cell (HSC) engraftment requires efficient homing to and seeding in the recipient bone marrow (BM). Dissection of cellular and molecular mechanisms by retrospective analysis of functional engraftment studies imposes severe limitations on the understanding of the early stages of this process. We have established a new experimental approach for in vivo functional imaging of PKH-labeled cells at the level of recipient BM microenvironment, in real time. An optical window is placed over the distal femur of mice, and labeled cells injected into a peripheral vein are tracked by fluorescence microscopy. The physiological competence of the procedure was assessed in a series of control experiments. (a) Blood supply is not compromised and BM infrastructure is not damaged, as determined from histology and viability tests. (b) Labeling with PKH dyes does not impair the function of HSC. (c) PKH-labeled cells were tracked for 3 weeks in the host femoral BM through the optical window (n = 36). (d) The number of HSC visualized through the optical window at magnifications of × 10–20 can be quantified. (e) In vivo observations were validated by optical analysis of naive femurs 1, 3, 6, and 12 days after injection of PKH-labeled HSC, and by durable, multilineage hematopoietic chimerism at 4 months. The behavior of HSC in windowed and naive femurs was qualitatively and quantitatively identical. The major limitations of the procedure are (a) time-consuming technique; (b) the field of view is obliterated by callus formation after 3 weeks; (c) photobleaching of the PKH dyes and dilution due to cell division; (d) in vivo observations need to be continuously validated by analysis of naive femurs to determine the impact of bone repair on the BM microenvironment. In vivo optical imaging is particularly suitable to study the mechanisms of early HSC engraftment, quantify gene delivery in HSC, and monitor graft-versus-host reactions in the BM.